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Longitudinal Analysis of Long-Term Air Pollution Levels and Blood Pressure: A Cautionary Tale from the Multi-Ethnic Study of Atherosclerosis

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Background: Air pollution exposures are hypothesized to impact blood pressure, yet few longitudinal studies exist, their findings are inconsistent, and different adjustments have been made for potentially distinct confounding by calendar time and age.

Objective: We aimed to investigate the associations of long- and short-term $PM_{2.5}$ and NO_2 concentrations with systolic and diastolic blood pressures and incident hypertension while also accounting for potential confounding by age and time.

Methods: Between 2000 and 2012, Multi-Ethnic Study of Atherosclerosis participants were measured for systolic and diastolic blood pressure at five exams. We estimated annual average and daily $PM_{2.5}$ and NO_2 concentrations for 6,569 participants using spatiotemporal models and measurements, respectively. Associations of exposures with blood pressure corrected for medication were studied using mixed-effects models. Incident hypertension was examined with Cox regression. We adjusted all models for sex, race/ethnicity, socioeconomic status, smoking, physical activity, diet, season, and site. We compared associations from models adjusting for time-varying age with those that adjusted for both time-varying age and calendar time.

Results: We observed decreases in pollution and blood pressures (adjusted for age and medication) over time. Strong, positive associations of long- and short-term exposures with blood pressure were found only in models with adjustment for time-varying age but not adjustment for both time-varying age and calendar time. For example, 16-ppb higher annual average NO_2 concentrations were associated with 2.7 (95% CI: 1.5, 4.0) and −0.8 (95% CI: −2.6, 1.0) mmHg in systolic blood pressure with and without additional adjustment for time, respectively. Associations with incident hypertension were similarly weakened by additional adjustment for time. Sensitivity analyses indicated that air pollution did not likely cause the temporal trends in blood pressure.

Conclusions: In contrast to experimental evidence, we found no associations between long- or short-term exposures to air pollution and blood pressure after accounting for both time-varying age and calendar time. This research suggests that careful consideration of both age and time is needed in longitudinal studies with trending exposures. https://doi.org/10.1289/EHP2966

Introduction

Over the past few decades, numerous studies have demonstrated associations of fine particulate matter (≤2.5 micrometers in aerodynamic diameter; $PM_{2.5}$) and traffic-related pollutants [e.g., nitrogen dioxide (NO_2)] with increased hospital admissions, morbidity, and mortality for cardiovascular diseases (Brook et al. 2010). Characterizing the mechanisms underlying these associations, however, remains an active area of research. Existing evidence suggests that long-term air pollution exposures increase the risk of cardiovascular events at least partially through the development of well-known risk factors such as diabetes, hypertension, inflammation, and endothelial dysfunction and through established processes such as atherosclerosis (Brook et al. 2010; Brook 2017; Bruno et al. 2017; Cosselman et al. 2015).

In recent years, a growing epidemiological and experimental literature has explored associations between air pollution and blood pressure (Giorgini et al. 2016). In animal and controlled-exposure studies in humans, short-term exposures to air pollution have been shown to increase blood pressure (Sun et al. 2008; Vieira et al. 2017; Ying et al. 2014; Cosselman et al. 2012; Kampfrath et al. 2011; Lucking et al. 2011) likely via short-term shifts in autonomic tone, endothelial activation, or oxidative stress and inflammation. At the population level, several studies have provided evidence that higher exposures to air pollution over a few days are associated with higher blood pressure levels (Auchincloss et al. 2008; Brook and Rajagopalan 2009; Brook et al. 2009; Dvonch et al. 2009; Urch et al. 2005; Zanobetti et al. 2004) although these findings have not been replicated in all studies (Harrabi et al. 2006; Ibald-Mulli et al. 2004; Jansen et al. 2005). Similarly, several studies have reported evidence that greater long-term air pollution levels (averaged over ≥1 y) are cross-sectionally associated with higher blood pressures (Auchincloss et al. 2008; Chan et al. 2015; Chuang et al. 2010; Chen et al. 2015; Dong et al. 2013; Foraster et al. 2014; Fuks et al. 2011, 2017) and more prevalent hypertension (Babisch et al. 2014; Bangia et al. 2015; Cai et al. 2016; Chen et al. 2014; Coogan et al. 2012; Dong et al. 2013; Fuks et al. 2017; Johnson and Parker 2009; Lin et al. 2017; Stanković and Nikolić 2016). However, other studies reported no, inverse, or inconsistent associations (Babisch et al. 2014; Chen et al. 2015; Levinsson et al. 2014; Sørensen et al. 2012). Similar to short-term exposures, these chronic effects are hypothesized to have roots in altered autonomic nervous system balance, vascular tone, or

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systemic inflammation (Giorgini et al. 2016). Two studies and a meta-analysis have suggested that for certain pollutants associations may be stronger for longer-term exposure, on the order of months or years, than for shorter exposures (Auchincloss et al. 2008; Liang et al. 2014; Schwartz et al. 2012). Because most studies on long-term exposures to air pollution and blood pressure have employed cross-sectional designs or focused exclusively on between-person contrasts, however, evidence for causality remains limited.

Longitudinal study designs are useful for ensuring that past air pollution exposures can be investigated in relation to future blood pressure levels. These designs also minimize the impacts of between-person confounding, thereby more closely getting at the causal question: Are changes in air pollution exposures over time related to changes in blood pressure levels? The steady declines in air pollution levels in the United States and abroad over the past 20 y make this a question of particular importance. However, longitudinal analyses of exposures that are changing over time require sufficient adjustment for temporal trends in other risk factors when the outcome is also trending over time, as is the case for blood pressure levels (Danaei et al. 2011). Yet the few existing longitudinal studies of blood pressure levels (Schwartz et al. 2012) and incident hypertension (Coogan et al. 2016; Honda et al. 2017; Sørensen et al. 2012; Zhang et al. 2016) have been largely inconsistent in both findings and their adjustment for potential confounding by age and time. In addition, existing analyses have often defined hypertension by self-report.

In this study, we used repeated measures of blood pressure and hypertension medication use collected between 2000 and 2012 at five clinical examinations from participants of the prospective Multi-Ethnic Study of Atherosclerosis (MESA) to study associations with air pollution. We aimed to investigate the associations of long- and short-term $PM_{2.5}$ and NO_2 concentrations with systolic and diastolic blood pressures as well as with incident hypertension. To estimate these associations, we compared models with adjustment for confounding by time-varying age to models adjusted for both time-varying age and calendar time.

Methods

Study Participants

As has been described in detail previously (Bild et al. 2002), MESA is a prospective cohort study designed to investigate predictors of subclinical cardiovascular disease. Between 2000 and 2002, MESA recruited 6,814 men and women, aged 45 to 84 y who were free of clinical cardiovascular disease, weighed <136 kg (<300 lb), and had no impediments to long-term participation. Participants were recruited from six U.S. communities (Forsyth County, North Carolina; Northern Manhattan and the Bronx, New York; Baltimore City and Baltimore County, Maryland; St. Paul, Minnesota; Chicago, Illinois; and Los Angeles County, California) to attend five clinical examinations that occurred in 2000–2002 (baseline), 2002–2004, 2004–2005, 2005–2007, and 2010–2012. Institutional review boards from all of the participating institutions approved the study and participants provided written informed consent.

For our analytic data sets, we restricted our population to only those participant visits with information on air pollution, key covariates, and blood pressure. In our analysis of incident hypertension, we further restricted the population to participants without prevalent hypertension at baseline.

Blood Pressure and Hypertension

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured at all five examinations after participants had rested for 5 min in the seated position. Blood pressures were measured with three replicates using an automated oscillometric sphygmomanometer (Dinamap Pro 100, GE Medical Systems Information Technologies, Inc.), with the average of the second and third readings used for analysis (Perloff et al. 1993). Participants were classified as hypertensive if they had an SBP ≥140 mmHg, a DBP ≥90 mmHg, or were taking antihypertensive medication as identified on exam-specific technician-administered questionnaires and visual inspection of medication bottles. We defined incident hypertension as a new classification of hypertension at one of the follow-up visits among participants who were free of hypertension at baseline.

Air Pollution

Residential $PM_{2.5}$ and NO_2 concentrations were estimated for each participant's address using spatiotemporal models developed by the MESA Air Pollution study (MESA Air) (Kaufman et al. 2012). Described in detail elsewhere (Keller et al. 2015), these models were derived using daily $PM_{2.5}$ and NO_2 concentrations collected from the U.S. Environmental Protection Agency (EPA) Air Quality System (AQS) along with an intensive monitoring campaign of samples collected in the communities and at the homes of the MESA cohort. These measurements were combined with relevant geographic covariates such as land use, local emission sources, and population density at or near participants' home addresses and the correlation of concentrations across space to estimate concentrations. To estimate exposures, we averaged our predictions over the 30 d, 60 d (medium-term exposures), and 1 y (long-term exposure) preceding each clinical examination. Because the smallest time resolution for the spatiotemporal model was 2 weeks, we estimated shorter-term exposures for the day and week before each examination using areawide average concentrations at all regional AQS monitoring stations within 75 km of MESA participants that were continuously collecting daily $PM_{2.5}$ measurements from July 1999 through the end of 2011.

Covariates

Detailed information on age; sex; race/ethnicity; tobacco smoke exposure; physical activity; education; dietary sodium, calcium, and fiber intake; and medications was collected using interviewer-administered questionnaires at baseline and/or follow-up visits. Medication use was further confirmed by visual inspection of medication bottles. Tobacco smoke exposure was categorized into groups based on self-reports of active smoking behaviors and exposure to environmental tobacco smoke, whereas hours per day of physical activity was categorized into quartiles. Height and weight were measured during each of the clinical exams and used to calculate body-mass index (BMI). Serum samples were also collected at baseline and follow-up exams and evaluated for fasting serum glucose, high-density lipoprotein cholesterol (HDL), total cholesterol, and triglycerides. We defined fasting glucose status as normal (≤5.6 mmol/L without use of hypoglycemic medications), impaired (5.6–6.9 mmol/L without use of hypoglycemic medications), or diabetic (≥7 mmol/L or use of any hypoglycemic medication) based on the American Diabetes Association criteria (Genuth et al. 2003). We also collected temperature and relative humidity data from the National Oceanic and Atmospheric Administration (National Climatic Data Center 2004) and estimated a neighborhood socioeconomic scale (NSES) for participants using census tract data including median household income, percentage of persons in tract with at least a high school degree, and median home value (Hajat et al. 2013).

Statistical Analysis

Our primary hypothesis is that the impacts of air pollution on blood pressure are transient and not irreversible alterations to disease progression. Therefore, we constructed linear mixed-effects models to estimate the associations of time-varying air pollution concentrations (X_{it}) with continuous SBP and DBP levels (Y_{it}) for each participant, i, and exam, t, while adjusting for time-invariant (Cov_{i0}) and variant covariates (Cov_{it}) (Equation 1). In our primary models, we adjusted for both time-varying age (Age_{it}) and calendar time ($Time_{it}$) to capture both aging and populationwide period effects (Jacobs et al. 1999). This is important given that air pollution and blood pressure levels, independent of age and medication (Chobanian et al. 2003), have both been declining over time. (We are able to disentangle time-varying age and calendar time in this study because participants entered the cohort at different ages [Pearson rho between age and time: 0.26]). Finally, our models were adjusted for within-subject correlations using random intercepts (b_i) and random slopes for age (α_i).

$$Y_{it} = \beta_0 + b_i + \alpha_i Age_{it} + \beta_1 X_{it} + \beta_2 Age_{it} + \beta_3 Time_{it} + \beta_0{}^T Cov_{i0} + \beta_\tau{}^T Cov_{it} + \varepsilon_{it} \quad (1)$$

In order to account for the effects of medication on blood pressure, we followed the methodologic literature and considered pretreated blood pressure for persons on antihypertensive medications as missing. Hence, multiple imputations were constructed and used in our main analyses (McClelland et al. 2008, 2013). We compared these results to those using observed blood pressure measurements with different statistical adjustments for medication use: restriction to participants not on antihypertension medications and the addition of a fixed blood pressure (mmHg) for participants on antihypertensive medications (Tobin et al. 2005).

We modeled associations between long-term pollution and incident hypertension using the Cox proportional hazards model, with age at exam as the time scale. Because the occurrence of hypertension was assessed at each exam, we assumed that the onset of new hypertension occurred midway between the first observed date of hypertension and the date of the previous exam. Results from this approach were consistent with interval-censored models performed in sensitivity analyses.

Potential confounders were identified *a priori* based on previously reported associations with blood pressure and the risk of hypertension. Our primary models adjusted for sex, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, and Chinese), education (≤high-school degree, some college or associate degree, or ≥bachelor's degree), study site, neighborhood socioeconomic status, and neighborhood socioeconomic status interacted by study site as time-invariant factors. We also adjusted for age at exam, calendar time, BMI, waist-to-hip ratio, tobacco smoke exposure, season (and season by site interaction), and physical activity as time-varying factors. Our models of acute exposures were further adjusted for relative humidity and temperature. Nonlinear relationships of the covariates and exposures with continuous blood pressure levels were explored graphically, with the degrees of freedom for our final models derived from the optimal fits from penalized splines. As a result, we added square terms into the model for BMI and waist-to-hip ratio. We modeled age using a linear trend for SBP and using a B-spline with 6 degrees of freedom for DBP. We modeled calendar time using B-splines with 4 and 6 degrees of freedom for SBP and DBP, respectively. All other covariates were modeled as linear.

Each averaging period and pollutant was explored separately in our primary models, but we examined a model of long- and short-term exposures in the same model in secondary analyses. We similarly explored multipollutant models. All estimates were reported for an interquartile range (IQR) of pollution and modeling was conducted using SAS software (version 9.3; SAS Institute) and R (version 3.4.4; R Development Core Team).

Sensitivity Analyses

Our primary analysis reflects our hypothesis that any impacts of air pollution on blood pressure are transient in nature. Nonetheless, we added to Equation 1 an interaction of time-varying age ($\beta_4 Age_{it} \times X_{it}$) with long-term pollution exposures as well as covariates ($\beta_{02} Age_{it} \times Cov_{0t} + \beta_{t2} Age_{it} \times Cov_{it}$) to explore whether high levels of air pollution over the previous year modified the blood pressure aging trajectories.

In other sensitivity analyses of our blood pressure analyses, we attempted to examine if we overadjusted for time in our models by including both time-varying age and calendar time. Overadjustment could occur if any trends in blood pressure are fully attributable to trends in air pollution. Although it is challenging to test this directly, we examined whether blood pressure trends were correlated with pollution changes after adjustment for confounders. Specifically, we adjusted for all covariates of interest except air pollution and evaluated the trends in blood pressure among individuals with steep decreases in exposure (>1 unit per y), modest decreases (>0 and ≤1 unit per y), or no decreases/increases (>0 units per y). If reductions in blood pressure over time were causally attributable to air pollution, then we would expect the steepest blood pressure drops to be among those with the steepest drops in pollution and not present among those with stable or increasing concentrations. We also investigated whether time trends in blood pressure were driven by within- or between-person variation by creating spaghetti plots and estimating cross-sectional associations from analyses stratified separately by exam and age to minimize confounding through restriction. We also examined fixed-effects models, in which we were able to estimate the associations of pollution after adjustment for age and time within a distribution of mean-centered blood pressure levels from each individual subject.

Finally, given loss-to-follow-up over the 12-y duration of the study, we examined the sensitivity of our modeling of both continuous blood pressure and incident hypertension to selective attrition using inverse probability weighting (Weuve et al. 2012). In addition, we re-ran all of our models to examine the impacts of additional adjustment for diabetes, cholesterol, triglycerides, dietary sodium, calcium, season, and fiber as well as differing degrees of freedom for our nonlinear relationships. We also looked for effect modification by age, sex, race/ethnicity, diabetes, obesity (BMI ≥30), and study site, examining the precision and parameter estimate of the interaction between $PM_{2.5}$ and the hypothesized effect modifier in our models.

Results

At baseline, our population of 5,587 individuals with complete data had an average age of 62 y, were 53% female, and were mostly nonsmokers (Table 1). The study population was approximately 30% black, 25% Hispanic, 10% Chinese, and 40% white. Among those 3,203 participants without hypertension at baseline, 1,320 developed hypertension over a median follow-up period of 6.4 y at a rate of approximately 70 new cases per 1,000 person-years. At baseline, mean SBP and DBP levels were 127 and 72 mmHg, respectively. Mean annual average $PM_{2.5}$ and NO_2 concentrations were 17 $\mu g/m^3$ and 22 ppb, respectively. Daily pollution exposures had similar average values but were more variable, such that the correlations between daily and annual averages were modest at 0.3 and 0.5 for $PM_{2.5}$ and NO_2, respectively (see Table S1).

Table 1. Selected participant characteristics by MESA examination [mean ± SD or *n* (%)].[a]

Characteristic	Exam 1 2000–2002	Exam 2 2002–2004	Exam 3 2004–2005	Exam 4 2005–2007	Exam 5 2010–2012
Total *n*	5,587	5,429	4,889	4,243	3,330
Demographics					
Age (y)	62.4 ± 10.2	63.6 ± 10.2	64.9 ± 10.1	66.3 ± 9.9	69.9 ± 9.5
Female	2,949 (53)	2,851 (53)	2,585 (53)	2,261 (53)	1,768 (53)
Male	2,638 (47)	2,578 (47)	2,304 (47)	1,982 (47)	1,562 (47)
Race/ethnicity					
White	2,073 (37)	2,097 (39)	1,922 (39)	1,607 (38)	1,264 (38)
Chinese	727 (13)	645 (12)	593 (12)	545 (13)	437 (13)
Black	1,527 (27)	1,459 (27)	1,320 (27)	1,119 (26)	861 (26)
Hispanic	1,260 (23)	1,228 (23)	1,054 (22)	972 (23)	768 (23)
Education					
<High school	1,038 (19)	940 (17)	807 (17)	682 (16)	493 (15)
High School	1,034 (19)	1,001 (18)	892 (18)	771 (18)	564 (17)
College Degree	2,527 (45)	2,506 (46)	2,267 (46)	1,972 (46)	1,582 (48)
>College	988 (18)	982 (18)	923 (19)	818 (19)	691 (21)
Missing	23	18	15	14	8
Smoking exposure					
Never smoker	2,845 (51)	2,497 (46)	2,230 (46)	1,960 (46)	1,554 (47)
Former smoker	2,042 (37)	2,320 (43)	2,142 (44)	1,881 (44)	1,534 (46)
Current smoker	700 (13)	612 (11)	517 (11)	402 (9)	242 (7)
Missing	22	44	42	66	65
Health variables					
BMI (kg/m^2)	28.2 ± 5.4	28.3 ± 5.5	28.3 ± 5.6	28.3 ± 5.6	28.4 ± 5.7
Diabetes					
Yes	719 (13)	806 (15)	744 (15)	732 (17)	665 (20)
No	4,868 (87)	4,623 (85)	4,145 (85)	3,511 (83)	2,665 (80)
Missing	24	45	51	156	121
Total cholesterol (mg/dL)	194.0 ± 35.9	191.1 ± 35.6	188.2 ± 36.2	187.6 ± 37.2	183.1 ± 37.2
Blood pressure variables					
Measured SBP (mmHg)	126.8 ± 21.5	124.4 ± 20.9	123.1 ± 20.7	123.3 ± 20.5	124.0 ± 20.6
Imputed SBP (mmHg)	129.6 ± 20.7	128.4 ± 20.4	128.4 ± 20.4	129.2 ± 20.4	131.6 ± 20.0
Measured DBP (mmHg)	71.9 ± 10.2	70.5 ± 10.1	69.7 ± 10.0	69.6 ± 10.0	68.0 ± 10.0
Imputed DBP (mmHg)	73.7 ± 9.8	72.8 ± 9.7	72.7 ± 9.5	72.7 ± 9.4	72.1 ± 9.2
Hypertensive[b]					
Yes	3,239 (50)	441 (14)	292 (12)	247 (12)	340 (22)
No	3,203 (50)	2,635 (86)	2,137 (88)	1,876 (88)	1,185 (78)
Missing	0	63	48	122	63
Hypertension medication					
Yes	2,082 (37)	2,187 (42)	2,213 (46)	1,998 (48)	1,844 (55)
No	3,503 (63)	3,008 (58)	2,601 (54)	2,122 (52)	1,486 (45)
Missing	3	261	102	187	8
Site					
Winston-Salem, NC	902 (16)	860 (16)	724 (15)	444 (10)	416 (12)
New York	831 (15)	917 (17)	851 (17)	827 (19)	634 (19)
Baltimore, MD	779 (14)	809 (15)	733 (15)	616 (15)	371 (11)
St. Paul, MN	809 (14)	891 (16)	802 (16)	676 (16)	547 (16)
Chicago, IL	1,013 (18)	845 (16)	903 (18)	812 (19)	739 (22)
Los Angeles, CA	1,253 (22)	1,107 (20)	876 (18)	868 (20)	623 (19)
Pollution					
$PM_{2.5}$ ($\mu g/m^3$)					
1 d	16.8 ± 10.2	15.5 ± 9.3	14.4 ± 8.7	13.7 ± 8.2	10.7 ± 5.7
2 d	16.6 ± 9.2	15.3 ± 8.3	14.3 ± 7.8	13.7 ± 7.4	10.8 ± 5.1
7 d	16.8 ± 6.9	15.5 ± 6.4	14.3 ± 5.8	13.6 ± 5.4	10.8 ± 3.6
30 d	16.3 ± 5.1	15.2 ± 4.8	13.9 ± 3.7	13.7 ± 3.8	10.8 ± 2.8
60 d	16.2 ± 4.6	15.3 ± 4.3	13.9 ± 3.2	13.8 ± 3.4	10.9 ± 2.5
1 y	16.7 ± 3.6	15.5 ± 3.4	14.5 ± 3.0	14.3 ± 2.4	11.2 ± 1.4
NO_2 (ppb)					
1 d	24.5 ± 13.4	23.5 ± 12.5	20.2 ± 11.1	20.2 ± 11.1	20.6 ± 11.2
2 d	23.8 ± 13.2	22.7 ± 12.6	19.4 ± 10.7	20.2 ± 11.0	19.9 ± 11.0
7 d	25.5 ± 13.6	24.2 ± 12.8	20.9 ± 11.1	21.6 ± 11.2	21.2 ± 11.1
30 d	21.5 ± 9.6	20.8 ± 9.6	18.5 ± 8.5	19.1 ± 8.6	14.8 ± 8.5
60 d	21.6 ± 9.5	20.8 ± 9.5	18.8 ± 8.5	19.1 ± 8.6	14.9 ± 8.4
1 y	21.8 ± 9.2	20.7 ± 9.1	19.6 ± 8.2	19.4 ± 8.1	15.6 ± 7.7

Note: BMI, body-mass index; DBP, diastolic blood pressure; $PM_{2.5}$, particulate matter less than 2.5 μm in aerodynamic diameter; SBP, systolic blood pressure.

[a]Unless indicated in table or footnote, there were no missing values. For continuous variables with missing, the number of missing for Exams 1–5, respectively, were as follows: BMI (0, 2, 8, 116, 74); cholesterol (23, 48, 55, 184, 134); SBP and DBP (3, 3, 11, 120, 63); Imputed SBP and DBP (3, 3, 11, 120, 69) $PM_{2.5}$ (766, 471, 579, 768, 742); and NO_2 (637, 270, 459, 867, 893).

[b]For our incident hypertension analyses we did not restrict to individuals without short- and medium-term exposure estimates. Therefore the counts presented here are larger than those in the rest of the table, which are for the blood pressure analysis.

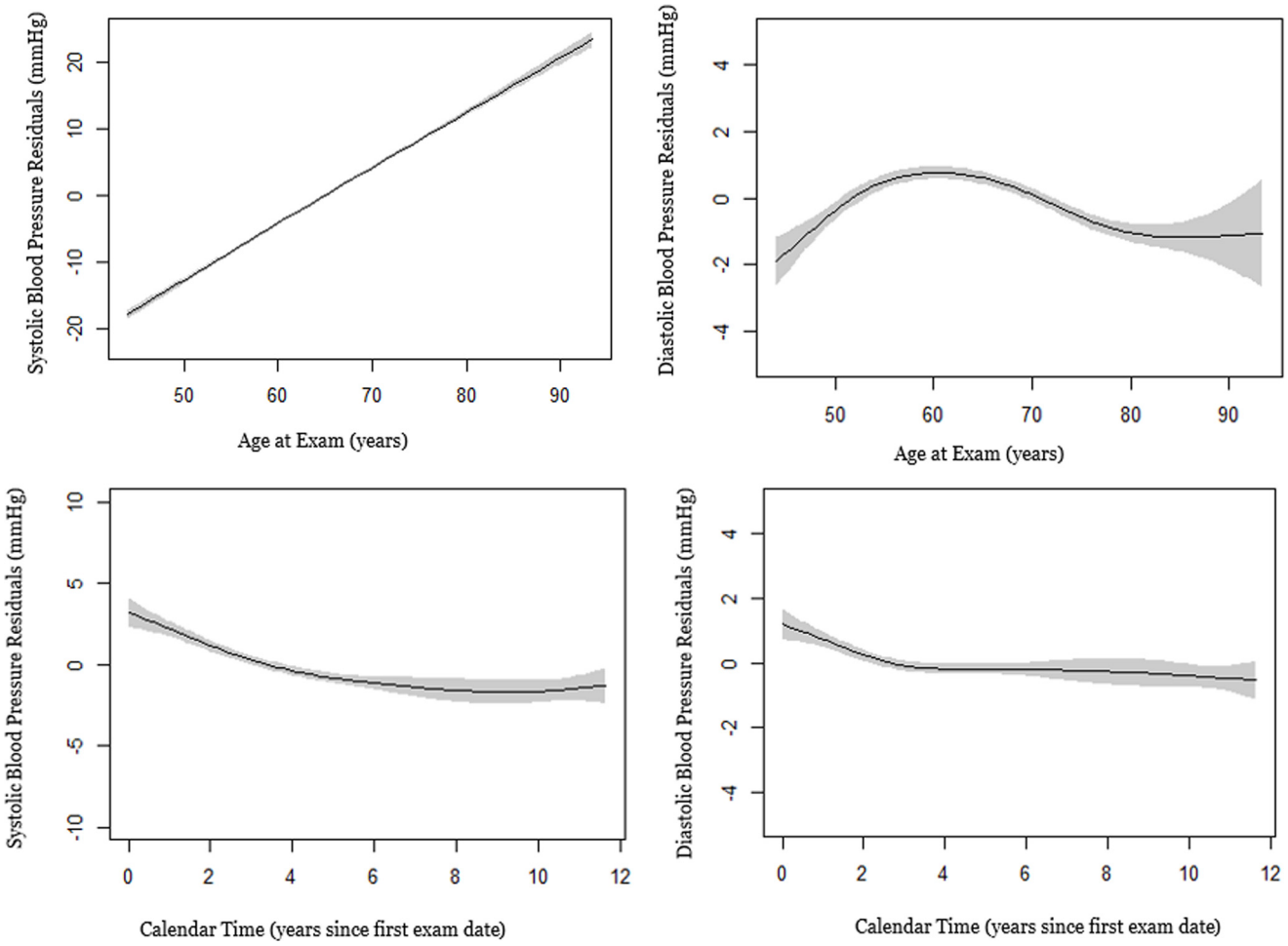

Figure 1. Trends in adjusted systolic and diastolic blood pressures due to both time-varying age and calendar time. Residuals of adjusted blood pressures outputted from a model of medication adjusted blood pressures after control for either calendar time or age and covariates (sex, race/ethnicity, education, study site, neighborhood socioeconomic status and its interaction with study site, season and its interaction with study site, body-mass index, waist-to-hip ratio, tobacco smoke exposure, and physical activity as well as random slopes and intercepts for subject). Gray bands are 95 confidence intervals.

Participants with complete information on outcome, covariate and 1-y exposures declined over time with 96, 92, 85, and 68% of the baseline population in Exams 2 through 5, respectively. After further restriction to those with non-missing short-and medium-term (<60-d) exposures, which was dependent on aworking central site monitor, about 60% of base-line subjects had complete data at Exam 5. (Table 1). Persons who were more educated, non-Hispanic, and nonhypertensive at baseline were more likely to have complete data at later exams.

Independent of other time-varying risk factors including BMI, waist-to-hip ratio, sodium consumption, physical activity, diabetes, and medication use, we observed independent trends in SBP and DBP levels with increasing time-varying age and calendar time (Figure 1). Added adjustment for diuretics, alpha blockers, beta blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin type 2 antagonists (see Figure S1) as well as restriction to individuals not on medications produced similar results (see Figure S2). Air pollution concentrations also declined roughly linearly over the follow-up period, with annual average $PM_{2.5}$ concentrations falling from 17 to 11 $\mu g/m^3$ and mean NO_2 levels declining steadily from 21 to 15 ppb (see Figure S3).

Associations of SBP and DBP with $PM_{2.5}$ and NO_2 at different averaging periods are presented in Figures 2 and 3, respectively. In models adjusted for all risk factors, including time-varying age but not calendar time, we observed that higher $PM_{2.5}$ and NO_2 concentrations were associated with higher blood pressure levels. These associations increased with larger averaging periods such that an IQR-higher annual average $PM_{2.5}$ concentration (3.1 $\mu g/m^3$) was associated with 1.0 [95% confidence interval (CI): 0.6, 1.4]- and 0.4 (95% CI: 0.2, 0.6)-mmHg higher SBP and DBP, respectively. An IQR-higher NO_2 concentration (16 ppb) was associated with 2.7 (95% CI: 1.5, 4.0)- and 1.0 (95% CI: 0.3, 1.6)-mmHg higher SBP and DBP, respectively. Additional adjustment for calendar time, however, fully eliminated all associations (Figures 2 and 3). Results were similarly null in models adjusted for time-varying age after stratification by exam (see Figure S4). Our findings with incident hypertension followed the same pattern as with blood pressure. Greater levels of pollution were strongly associated with a greater risk of incident hypertension in models with adjustment for time-varying age but without calendar time. However, these associations were substantially blunted after adjustment for time (Table 2).

Sensitivity analyses did not support the hypothesis that air pollution was responsible for reductions in blood pressure levels over time. As shown in Figure 4, we found reductions in blood pressure even in participants who did not experience reductions in air pollution. In addition, we did not find steeper reductions in adjusted blood pressure levels among those with the largest reductions $PM_{2.5}$ or NO_2 (Figure 4; see also Figure S5). We also

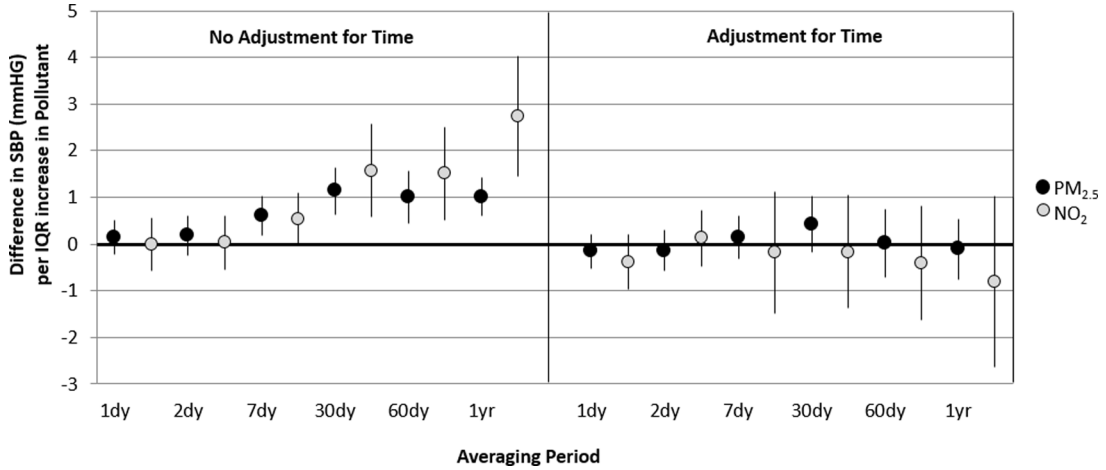

Figure 2. Associations (95% CI) of systolic blood pressures with $PM_{2.5}$ and NO_2 concentrations with and without additional adjustment for calendar time. Models adjusted for age at exam, sex, race/ethnicity, education, study site, neighborhood socioeconomic status and its interaction with study site, season and its interaction with study site, body-mass index, waist-to-hip ratio, tobacco smoke exposure, physical activity, and calendar time (as noted) as well as random slopes and intercepts for subject. Note: CI, confidence interval; IQR, interquartile range; $PM_{2.5}$, particulate matter less than 2.5 μm in aerodynamic diameter; SBP, systolic blood pressure.

found no associations between pollution and the rate of change of blood pressure over time, a model that inherently incorporates time (see Table S2).

In other sensitivity analyses, there was significant effect modification of associations between $PM_{2.5}$ and both outcomes by study site, but no significant differences in associations with SBP or DBP by gender, race/ethnicity, age, diabetes, or obesity (BMI ≥30) (see Figures S6 and S7). Interactions of $PM_{2.5}$ with gender and age were significant for DBP, but not SBP. We also found null associations with more and less control for other confounding factors (including diet, class of hypertensive medication, and physical activity), alternate parameterizations of age and time, employment of fixed-effects models, and adjusting for loss-to-follow-up although there was some sensitivity of our findings to the use of different adjustment approaches for antihypertensive medications (see Figure S8).

Discussion

In this prospective cohort of older adults without clinical cardiovascular disease at baseline, we found evidence of reductions in blood pressure over the 12-y follow-up period independent of traditional risk factors. Given that air pollution levels were dropping over the same period, air pollution and blood pressure were associated in models that accounted for time-varying age but not calendar time. These associations were, however, eliminated by additional adjustment for calendar time. Because we found no correlations between changes in air pollution over time and changes in adjusted blood pressures over time, we concluded that control for calendar time was warranted. This work highlights the importance of including adjustment for both age and calendar time in longitudinal studies when trends in the exposure and outcome occur during the follow-up period.

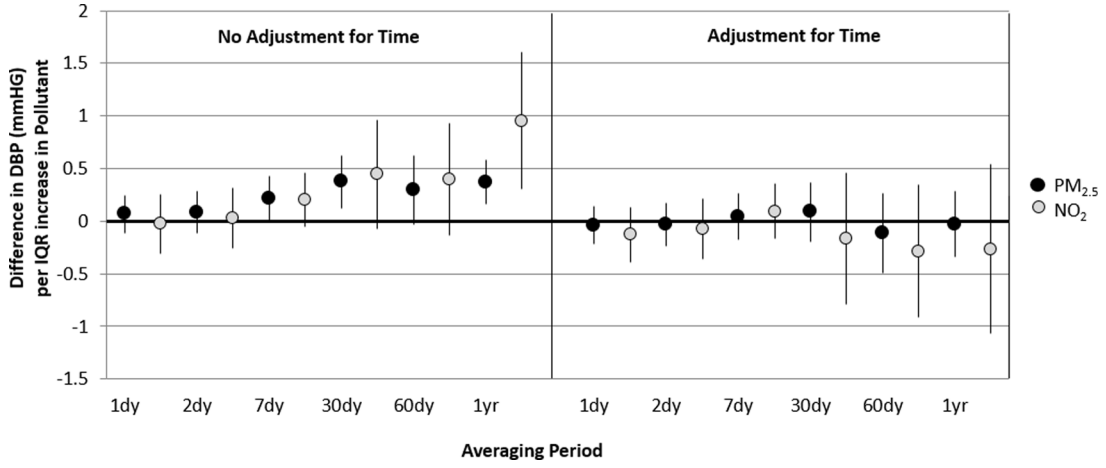

Figure 3. Associations (95% CI) of diastolic blood pressures with $PM_{2.5}$ and NO_2 concentrations with and without additional adjustment for calendar time. Models adjusted for age at exam, sex, race/ethnicity, education, study site, neighborhood socioeconomic status and its interaction with study site, season and its interaction with study site, body-mass index, waist-to-hip ratio, tobacco smoke exposure, physical activity, and calendar time (as noted) as well as random slopes and intercepts for subject. Note: CI, confidence interval; DBP, diastolic blood pressure; IQR, interquartile range; $PM_{2.5}$, particulate matter less than 2.5 μm in aerodynamic diameter.

Table 2. Hazard ratios (HRs) of incident hypertension associated with an interquartile range in annual average $PM_{2.5}$ and NO_2 concentrations.

	$PM_{2.5}$			NO_2		
Model[a]	HR	95 CI	*p*-Value	HR	95 CI	*p*-Value
Minimal	1.05	(0.99, 1.11)	0.10	1.00	(0.90, 1.02)	0.99
+ Risk factors	1.08	(1.02, 1.14)	0.01	1.08	(0.97, 1.21)	0.16
+ Site	1.28	(1.16, 1.42)	<.0001	1.51	(1.19, 1.93)	0.00
+ Time	1.05	(0.93, 1.19)	0.40	1.13	(0.88, 1.47)	0.34

Note: These models are built sequentially so that each model contains all covariates in the previous row. For example, our + Time model includes all minimal, risk factor, site, and time adjustments. BMI, body-mass index; CI, confidence interval; HR, hazard ratio; NSES, neighborhood socioeconomic scale; $PM_{2.5}$, particulate matter less than 2.5 μm in aerodynamic diameter.

[a]Minimal: gender, race; + Risk factors: education, NSES, smoking exposure, physical activity, waist-to-hip ratio, BMI; + Site: study site, study site x NSES; + Time: calendar time.

The presence of period effects in blood pressure independent of aging had a profound impact on our results. These generally downward trends in blood pressure could not be explained by changes in measurement equipment or approach, selective attrition, or time-varying risk factors including age, adiposity, diet, physical exercise, and medication use. They were also observed both in fully cross-sectional and within-person analyses. Although somewhat surprising, this is not the first study to document such trends in the United States and globally (Danaei et al. 2011). One possible explanation for these trends is changes in efficacy of antihypertension medications or prescribing practices by physicians. In fact, shifts in the diuretic prescriptions in MESA participants was documented following the publication of the clinical Antihypertensive Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) (Delaney et al. 2009). Yet multiple adjustment approaches for medications could not completely explain these trends. This may reflect the challenges of accounting for medication even when detailed data is available or it may imply another unknown cause of these trends.

Because air pollution concentrations have also been declining over time with stricter air quality regulations, we investigated the possibility that reductions in air pollution were responsible for these unexplained reductions in blood pressures. If this were the case, then we would expect to observe the steepest blood pressure reductions among persons also experiencing the largest pollution reductions. We would also expect no drops in blood pressure among those with stable or increasing concentrations. However, this was not strongly supported by the data, suggesting that another unmeasured cause for blood pressure reductions confounds the relationships with air pollution. Importantly, air pollution is not the only risk factor for disease that has been changing over time. There are well-established trends in obesity (Finucane et al. 2011), cholesterol (Farzadfar et al. 2011), and smoking (Bilano et al. 2015), just to name a few. Thus, confounding by calendar time is an issue of general importance. Although the

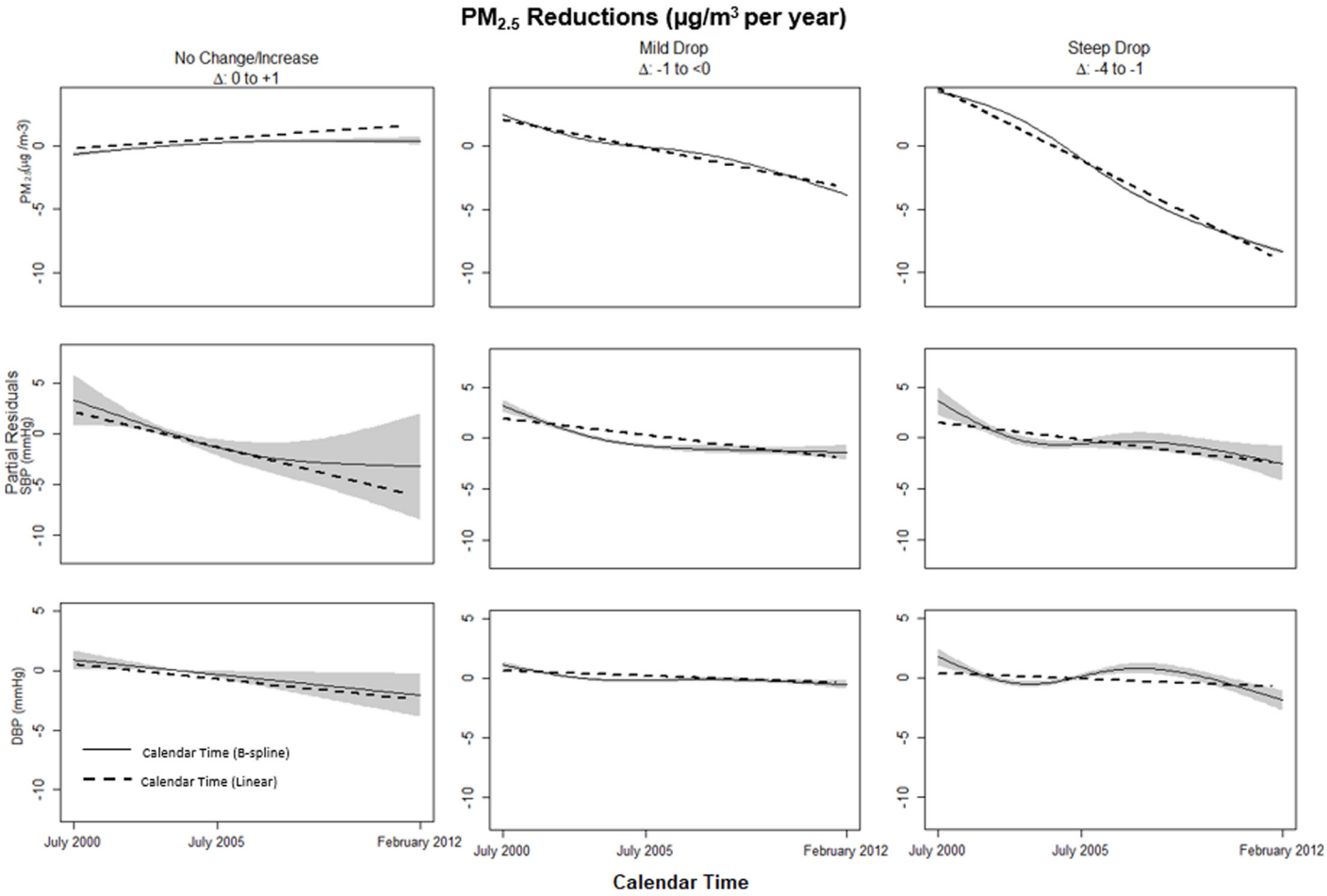

Figure 4. Trends in annual average $PM_{2.5}$ and adjusted blood pressure stratified by extent of air pollution reductions. Models adjusted for age at exam, sex, race/ethnicity, education, study site, neighborhood socioeconomic status and its interaction with study site, body-mass index, waist-to-hip ratio, tobacco smoke exposure, and physical activity as well as random slopes and intercepts for subject. Solid lines indicate an assumption of nonlinear trend using B-splines in calendar time. Note: DBP, diastolic blood pressure; $PM_{2.5}$, particulate matter less than 2.5 μm in aerodynamic diameter; SBP, systolic blood pressure. Dotted lines indicate an assumption of linear trend in calendar time.

impacts of this issue have been reported previously for Cox regression modeling (Griffin et al. 2012), our findings highlight the need for careful consideration of confounding by both time-varying age and calendar time when conducting any longitudinal modeling with time-varying exposures.

The availability of time-varying exposure estimates in MESA is a strength of our study but also introduced statistical challenges due to correlated trends over time between our exposure and outcome. Only a few other published investigations have examined changes in blood pressure and incident hypertension over time as a function of time-varying air pollution levels. In one of the first of these analyses, larger black carbon concentrations over the previous year were associated with greater blood pressure levels in repeated measures of 853 U.S. veterans sampled between 1996 and 2008 (Schwartz et al. 2012). Because time-varying age but not calendar time was accounted for in their models, however, it is possible that this may reflect an overestimate of the true association. In fact, another longitudinal study from Denmark (1993–2002) did adjust for both time-varying age and calendar time and found no evidence of an association between greater time-varying NO_x concentrations and higher risks of incident hypertension. Furthermore, they reported inverse associations with blood pressure levels after adjustment for time (Sørensen et al. 2012). A reanalysis of the Black Women's Health Study also recently reported null associations between incident hypertension and air pollution after controlling for age and time in 2-y blocks in spite of an earlier report of a positive association (Coogan et al. 2016). Another recent analysis from the Women's Health Initiative only identified associations between air pollution and incident hypertension with time-varying but not time-invariant exposures (Honda et al. 2017). Only the Nurse's Health Study reported greater odds of incident self-reported hypertension with higher levels of time-varying PM_{10} and $PM_{2.5}$ concentrations after adjustment for both age and time (Zhang et al. 2016).

It is important to note that confounding by calendar time can also occur in other designs that include time-varying exposures and outcomes collected over many years. Here, we demonstrate such confounding with longitudinal mixed-effects models, but this source of bias can also impact other designs. Cross-sectional studies using time-varying exposures may also be confounded by time if the health measurements have been collected over many years. Examples of studies that may be subject to this type of bias exist in the literature where outcomes were measured over more than 15 y and evaluated against time-varying exposures with adjustment for age but without adjustment for calendar time (Fuks et al. 2014; Johnson and Parker 2009; Zhang et al. 2018). Fixed-effects models or hybrid multi-level models that center all covariates to person-specific means can also be subject to this type of confounding. These methods are designed to estimate the impacts of time-variant exposures with outcome measures that have had time-invariant differences removed. However, separate adjustment will still be required for time-varying age and calendar time in this design if trends in the outcome are non-linear with these covariates.

In spite of a pattern of inconclusive findings with time-varying exposures, there are logical mechanistic links between long-term exposures to air pollution and elevated blood pressures (Brook and Rajagopalan 2009; Giorgini et al. 2016). For example, inhaled pollutants can trigger endothelial dysfunction and vasoconstriction of arterioles as well as vascular dysfunction and arterial vasoconstriction (Adar et al. 2010; Araujo 2010; Ghio et al. 2000; Kelly 2003; Krishnan et al. 2012; Peretz et al. 2008). Alterations to the vasoconstriction or resistance of these small blood vessels would be expected to raise DBPs. In contrast, impacts of air pollution on cardiac output by altering cardiovascular autonomic nervous system balance or increasing aortic stiffness (Luttmann-Gibson et al. 2006; Mehta et al. 2014; Park et al. 2005) would be expected to preferentially raise SBP levels. Several studies using time-invariant air pollution exposures that would not be subject to confounding by time have reported that greater long-term levels of air pollutants such as $PM_{2.5}$ and NO_2 are associated with greater levels of SBP (Chan et al. 2015; Chuang et al. 2010; Dong et al. 2013; Foraster et al. 2014) and DBP (Chan et al. 2015; Chuang et al. 2010; Dong et al. 2013; Fuks et al. 2011) as well as more hypertension (Babisch et al. 2014; Bangia et al. 2015; Chen et al. 2014; Coogan et al. 2012; Dong et al. 2013; Fuks et al. 2011; Stanković and Nikolić 2016). However, others reported no, inverse, or inconsistent associations (Chen et al. 2015; Foraster et al. 2014; Levinsson et al. 2014). Although the larger literature seems to generally support associations between air pollution and blood pressure, discrepancies between studies as well as our findings suggest that the evidence for this relationship remains inconclusive.

A major strength of this study was the MESA cohort with detailed, time-varying measures of health outcomes and confounders. In addition, this project had state-of-the-art, individual-level exposure estimates derived from spatiotemporal models using extensive project-specific measurements (Cohen et al. 2009; Szpiro et al. 2009). As with all modeled exposures, however, there is some inherent measurement error in our estimates (city-specific cross-validated R^2s ranging from 0.5 to 0.9 for both pollutants) that may influence the magnitude or significance of our findings (Szpiro and Paciorek 2013; University of Washington 2015). Another strength of the MESA is the long follow-up that allowed for the examination of associations between exposures and blood pressures and incident hypertension using repeated measurements while adjusting for both age and calendar time. This also introduced challenges with respect to confounding by time, as discussed previously. Although our results suggest that confounding by both age and calendar time was likely, it remains possible that we over-controlled for exposure by adjusting our models for time, thus minimizing our ability to detect an association. Our results may also have been influenced by selective attrition given that air pollution and hypertension are both related to morbidity and mortality for other cardiovascular diseases (Brook 2008; Narayan et al. 2010; Sowers et al. 2001; Weisskopf et al. 2015). Accounting for loss to follow-up using inverse probability weighting, however, did not support the finding that uneven loss to follow-up by exposure status was playing an important role in this study. Finally, the inclusion criteria of the MESA may also have played a role in the lack of an association between air pollution and blood pressure if older participants without cardiovascular diseases represent a healthier and less susceptible population for the effects of air pollution.

Conclusions

In summary, results from this observational study were inconsistent with the experimental literature in that we found no evidence of associations between long- or short-term exposures to ambient air pollutants and blood pressure. This work also highlighted the importance of a careful consideration of confounding by both time-varying age and calendar time in longitudinal studies with time-varying exposures and outcomes.

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